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NON-ALCOHOLIC FATTY LIVER DISEASE AND LIVER TRANSPLANTATION

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Summary:

Cirrhosis secondary to non-alcoholic steatohepatitis (NASH) is a common indication for liver transplant. In comparison to other cirrhotic patients, patients with NASH cirrhosis are more likely to be older and have the metabolic syndrome. Pre-transplant, patients require careful evaluation of cardiovascular risk.

As the incidence of non-alcoholic fatty liver disease (NAFLD) is rising, a greater proportion of donor grafts have steatosis greater than 30%, which is associated with poor outcomes. Grafts with steatosis greater than 60% are unsuitable for transplant.

Overall, post-transplant survival outcomes for patients with NASH cirrhosis are similar to those with cirrhosis without NASH. However, NASH cirrhosis is associated with a higher 30-day mortality, predominantly from an increase in cardiovascular events and infections.

Following liver transplant, there is a significant risk of NASH recurrence, although this seldom results in allograft loss. Furthermore, a significant number of patients who had a liver transplant for other reasons develop NASH *de novo*.

When patients with NASH cirrhosis are considered for transplant, one of the major challenges lies in identifying which patients are too high risk for surgery. This review aims to provide information to aid this decision making process, and to provide guidance on the peri-operative care strategies that can modify risk.

Introduction

NAFLD is common with an estimated global prevalence of 25% [1]. NAFLD encompasses a spectrum of pathology; whilst most patients have simple steatosis, around 7-30% have NASH, of which 10-20% progress to liver cirrhosis, for which the only treatment is liver transplantation [1].

Risk factors for NAFLD include the metabolic syndrome [1], increasing age and genetic polymorphisms, such as the patatin-like phospholipase domain-containing 3 (PNPLA3) gene variant I148M [2, 3]. The metabolic syndrome represents a collection of cardiovascular risk factors associated with insulin resistance such as central obesity, hypertension, dyslipidaemia and glucose intolerance/diabetes. Around 80% of patients with NAFLD have at least one component of the metabolic syndrome, with the likelihood of having NAFLD rising in proportion with the number of metabolic syndrome components present [4]. In high risk populations, such as the morbidly obese and patients with diabetes, the prevalence of NAFLD is reported to be 70-90% [5, 6].

As the incidence of obesity and diabetes is rising, so too is the incidence of NAFLD [7]. The proportion of liver transplants performed for NASH cirrhosis has increased from 1.2% in 2001 to 9.7% in 2009 [8], with NASH now the second

leading aetiological indication for liver transplant in the US [9], and is predicted to become the most common indication for transplant within the next 20 years [8].

Studies assessing the impact of NAFLD on mortality have shown mixed results. This may reflect variation in the inclusion criteria (deranged liver function tests vs ultrasound findings vs biopsy results), failure to account for NAFLD severity, and varying degrees of adjustment for confounding variables such as diabetes and obesity. In a meta-analysis, the adjusted hazard ratio (HR) for overall mortality in NAFLD compared to patients without NAFLD was 1.04 (95% confidence interval (CI) 1.03-1.04) [1], and thus whilst steatosis alone may not have a major impact on mortality risk, the degree of associated fibrosis does influence outcomes. Angulo et al performed retrospective analysis of laboratory and histological data on 691 patients diagnosed with NAFLD. The results showed that mortality risk was related to the degree of fibrosis, regardless of steatohepatitis or NAFLD activity (stage 1 HR 1.88 (95% CI 1.28-2.77), stage 2 HR 2.89 (95% CI 1.93-4.33), stage 3 HR 3.76 (,95% CI 2.40-5.89), stage 4 HR 10.9 (95% CI 6.06-19.62) [10]

In patients requiring liver transplantation, the increased prevalence of the metabolic syndrome in NAFLD complicates their operative work-up and will be reviewed in this article alongside their transplant outcome data. Notably, some patients with NAFLD develop recurrent disease after transplantation, alongside a proportion of non-NAFLD patients that develop *de no*vo NAFLD post-transplant.

In evaluating the data, two issues need to be considered. Firstly, NAFLD is a recently recognised entity and thus there is a paucity of long-term longitudinal follow-up data following transplantation, in comparison with other causes of liver cirrhosis. Secondly, it is difficult to obtain complete incidence and prevalence data for NAFLD, as by the time some NAFLD patients develop cirrhosis, many patients lose the typical histological features of NASH. Therefore, some cases of NASH cirrhosis are labelled as cryptogenic cirrhosis [11].

2. Pre-transplant considerations:

2.1 Indications for transplant

Liver transplant is an effective treatment for end-stage liver disease, with an overall one-year survival of around 91% and three-year survival of around 80% [12]. There are no disease-specific indications for transplantation in NAFLD; guidelines recommend that NAFLD patients be considered for liver transplant if they have evidence of NASH cirrhosis with end-stage liver disease or hepatocellular cancer [13]. The Model for End Stage Liver Disease (MELD) score can be used to evaluate disease severity in potential transplant candidates with NAFLD, similarly to cirrhosis from other causes.

The diagnosis of NASH cirrhosis is ideally obtained on histology, however, liver biopsy may not always be possible, for example in patients presenting with

decompensation. In that situation, if there is no other likely cause for cirrhosis, patients can be presumed to have NASH cirrhosis if they have three or more components of the metabolic syndrome[14].

2.2 Pre-operative risk stratification

2.2.1 NAFLD and cardiovascular disease (CVD)

Patients with NAFLD commonly have risk factors for CVD, including diabetes, hypertension, hyperlipidaemia and obesity [4, 15]. Further evidence links NAFLD to subclinical and clinical CVD. For example, it is associated with endothelial dysfunction, increased carotid artery intima thickness, increased arterial stiffness and elevated coronary calcium scores, coronary artery disease (CAD), aortic valve sclerosis and cardiac arrhythmias, such as atrial fibrillation [16-21]. The association of NAFLD with CAD may be secondary to endothelial dysfunction, a pro-atherogenic lipid profile, and/or unstable coronary artery plaques [22-24]. Furthermore, NAFLD is associated with myocardial dysfunction, a reduced ability to increase heart rate and cardiac output in response to stress, and an increased baseline cardiac output, resulting in cardiac hypertrophy ("cirrhotic cardiomyopathy")[25, 26]. Longitudinal studies suggest that cardiovascular disease is the most common cause of death in NAFLD [19, 27-30]

Approximately 27% of liver transplant candidates have undetected underlying CVD, and patients with CAD undergoing transplant have a one-year mortality exceeding 40% [31, 32]. Evaluation of cardiovascular risk in patients with NASH is important to identify which patients are likely to have poor postoperative outcomes and thus be unsuitable for transplant (Figure 1). It also allows the opportunity for pre-operative optimisation of cardiovascular risk factors. Risk evaluation includes history taking and examination to elicit signs and symptoms of coronary artery disease, and cardiovascular risk factors. All patients should undergo 12-lead electrocardiography (ECG), a chest X-ray (CXR) and a transthoracic echocardiogram (ECHO), to identify any underlying structural heart disease, left ventricular dysfunction and pulmonary hypertension [13]. Patients should also have an assessment of their functional capacity. Functional capacity reflects a patient's ability to perform aerobic work and is defined by the maximal oxygen uptake ($V0_2max$) when the patient is physically exhausted. Functional capacity is usually expressed in multiples of metabolic equivalents (METs), where 1 MET represents the resting energy expenditure, usually around 3.5ml oxygen/kg/min. Prior to major surgery, patients should ideally be able to perform >4 METs, which is roughly equivalent to climbing one flight of stairs without stopping. In clinical practice, this can be estimated using pulse oximetry following a witnessed climb of stairs, or a validated questionnaire, such as the Duke Activity Status Index [33]. More accurate results can be obtained using cardiopulmonary exercise testing (CPEX) with a cycle ergometer [34].

Following these baseline tests, in patients with suspected CAD, non-invasive testing can be used to decide on the need for a coronary angiogram (Figure 1). As patients with advanced liver disease may not be able to achieve maximal heart rate on exercise testing, American guidelines recommend dobutamine stress ECHO (DSE) testing instead in patients with suspected occult coronary disease[35]. However, studies suggest that, although widely used, DSE has a low predictive value for obstructive CAD on angiography [36, 37]. Nuclear perfusion

imaging also has a low positive predictive value for lesions on angiogram, and the use of drugs such as adenosine is potentially unsafe given the haemodynamic abnormalities associated with end stage liver failure [38]. Measurement of coronary calcium on computerised tomography (CT) is another non-invasive technique for estimating the degree of coronary plaque, and thus assessing cardiovascular risk. A 'calcium score' over 400 represents 'high risk' for cardiovascular events, and such patients may merit coronary angiography [39-41]. Low calcium scores can help to exclude significant CAD. Further studies are needed to determine its' cost-effectiveness in comparison with stress ECHO in liver transplant candidates.

Quantifying cardiovascular risk using stratification scores can potentially be used with non-invasive testing to decide on the appropriateness of angiography. The Framingham Risk Score is a well-established scoring system for predicting 10-year risk of angina, myocardial infarction and cardiac death. However, in end-stage liver disease patients this score is thought to underestimate risk [42]. Furthermore, the score was based on studies in an almost exclusively Caucasian population in America, and so it is unclear if the results can be extrapolated. Guckelberger et al used receiver operation characteristic (ROC) curve analysis to compare different cardiovascular risk scoring systems in liver transplant recipients. The Prospective Cardiovascular Munster Study (PROCAM) score was found to be better than the European Systematic Coronary Risk Evaluation (SCORE) and the Framingham Risk score (FRS) in distinguishing patients with high and low cardiovascular risk [43]. The variables considered in this scoring system were gender, age, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, smoking status, and family history of coronary artery disease. However, in their study over half of the patients were excluded from the analysis, which could potentially have biased the results, and there were few cardiovascular events overall. Therefore more studies are required before the widespread use of the PROCAM score can be advocated.

There are several additional scoring systems to estimate peri-operative cardiac risks but these have not been studied in liver transplant patients. The revised cardiac index includes six items- four relate to the patient's past medical history (CAD, heart failure, cerebrovascular disease, and diabetes mellitus), one relates to the risk of the planned procedure, and one relates to the creatinine level. This score can predict complications such as myocardial infarction, pulmonary embolism, complete heart block, ventricular fibrillation and cardiac arrest [44]. Use of troponin T measurements in conjunction with this score can improve risk stratification [45].

Once CAD is suspected or confirmed, there are medical and surgical management options. In patients with risk factors for CVD, initiation of cardioselective beta-blockers and statins prior to major surgery is effective in reducing cardiac mortality and myocardial infarction [46, 47]. Carvedilol has been shown to be better than other beta-blockers in reducing portal pressures, and therefore may be the drug of choice in end-stage liver disease [48, 49]. Use of beta-blockers in refractory ascites has been questioned recently due to a concern that they may increase mortality, although there is no clear consensus at this stage[50-52]. In

patients undergoing non-cardiac surgery, statins have been shown to reduce cardiovascular mortality by 44%, and their effects may be independent of their ability to lower cholesterol and driven by an anti-inflammatory effect and platelet modulatory function [53-55]. Simvastatin and atorvastatin interact with calcineurin inhibitors, whereas rosuvastatin has minimal interactions and is relatively more potent so would therefore be preferred choice of statin [56]. Studies of peri-operative statin and beta-blocker use in the context of liver transplantation are lacking.

Current American Guidelines recommend intervention for >70% stenosis on coronary angiography [35], yet it remains unproven whether this is the optimal 'cut off' for intervention. Yong et al found that in 21 patients with CAD who underwent liver transplant, those with multi-vessel disease (regardless of the degree of stenosis) had significantly higher mortality and post-operative length of stay than patients without multi-vessel disease (27% vs 4%) [57].

There are reports of coronary artery bypass grafting (CABG) being performed in patients awaiting liver transplant [58-60], but it is generally contraindicated in end-stage liver failure, as it can trigger decompensation of liver disease secondary to release of inflammatory mediators [61, 62]. In a case series of 27 patients, one-year survival following CABG was 80% in Child Pugh A, 45% in class B, and 16% in class C [63]. Small studies have shown percutaneous coronary intervention (PCI) in to be safe and feasible in end-stage liver disease [64], although these patients are at higher risk of bleeding complications [65]. In patients requiring coronary stenting, a bare metal stent may be preferable to avoid prolonged dual antiplatelet therapy, in view of the bleeding risks in liver failure and potential hepatotoxicity of clopidogrel [66].

Whether revascularisation prior to liver transplant actually alters outcomes remains contentious. In a cohort study of patients undergoing liver transplant, those with known CAD had a cardiac mortality of 50% over a 10 year follow up, despite pre-transplant intervention with CABG or PCI [67]. Similar findings were reported by Plotkin et al [58]. However, both studies were retrospective, with small sample sizes, and groups were not stratified according to CAD severity. Furthermore, relatively few of the patients underwent angiography, and so authors may have underestimated the presence of occult CAD in the 'no intervention' groups. Other studies have reported a possible beneficial effect of intervention; in a retrospective study of 630 patients by Wray et al, there was no difference in mortality between those with coronary artery stenosis >50% (n=151), and those without significant coronary artery stenosis (n=479), with current CAD treatment strategies applied pre-operatively [68]. Maddhur et al found a reduction in 1-year post-operative mortality rates over a ten year period, which coincided with an increase in the number of PCI procedures performed, although this could be affected by other confounding variables [31]. Ideally randomised controlled trials would be needed to confirm whether revascularisation prior to transplant improves outcomes.

Echocardiograms (ECHO) may identify sub-clinical abnormalities such as valvular disease, left ventricular dysfunction and pulmonary hypertension [13].

Symptomatic valvular disease is a contraindication to transplant, although pre-transplant left ventricular dysfunction is not an absolute contraindication to transplant, as it may improve post-operatively. However, it is important to ensure that such patients are on optimal medical therapy, including beta-blockers, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) [69]. In patients with concomitant renal dysfunction, these drugs should be used with caution. Patients with echocardiographic evidence of pulmonary hypertension should undergo right heart catheterisation to confirm the diagnosis. Those with moderate-severe pulmonary hypertension diagnosed on right heart catheterisation (mean pulmonary artery pressure≥ 25mmHg, pulmonary capillary wedge pressure ≤ 15mmHg and pulmonary vascular resistance of >3 Wood units) should be referred to a cardiologist. Repeat right heart catheterisation after a trial of pulmonary vasodilators may show improvement in parameters such that liver transplantation can proceed. Intra-operative monitoring of the liver transplant patient should include ECG, pulse oximetry and monitoring of blood pressure and cardiac output.

2.2.2 NAFLD and renal disease

NAFLD is an independent risk factor for renal disease [70]; compared to patients without NAFLD, patients with NAFLD have higher creatinine levels at baseline, and are more likely to develop stage III kidney disease after liver transplant (31% vs 8%)[8, 71, 72]. Renal impairment is one of the strongest predictors of post-transplant cardiovascular mortality and so is important to screen for [73].

Management of renal dysfunction in liver transplant candidates is discussed in an excellent article by Weber et al [74]. Patients with liver cirrhosis have lower serum creatinine levels than those without cirrhosis, which may relate to reduced creatinine production by the liver, or lower muscle mass for example [75]. However, creatinine measurement is widely available and inexpensive and therefore initial screening tests should include serum creatinine, urinalysis, quantitative protein measurement and renal ultrasound. If these tests are abnormal, measurement of glomerular filtration rate (GFR) using isotopes may be helpful to give a better idea of the true GFR [74]. If it is indeed low, kidney biopsy may help to determine the underlying aetiology.

In some patients, simultaneous liver-kidney (SLK) transplant may be performed. In patients who are not on dialysis pre-transplant, and have a serum creatinine <2mg/dL, SLK confers no additional survival benefit at 3 years over liver transplant alone (69.9% vs 69.8%) [76]. Following a consensus conference on SLK transplantation, it was suggested that SLK transplants are appropriate in (1) patients with end stage renal disease requiring a liver transplant (2) patients with acute kidney injury (serum creatinine >2mg/dL) on dialysis for over eight weeks (3) patients with chronic kidney disease with >30% interstitial fibrosis or >30% global glomerulosclerosis on renal biopsy [77]. Data between 2002 and 2011 from the United Network of Organ Sharing Database (UNOS) shows that NASH is the most rapidly growing indication for SLK transplantation [78], although outcomes are poor with a 1.5 fold higher risk of kidney graft loss than in patients having SLK for cholestatic or alcoholic liver disease [78].

2.2.3 NAFLD and obesity

Amongst obese patients, the estimated prevalence of NASH is 57-74% [79]. Obesity has many implications for patients with NASH cirrhosis undergoing transplant. In a study of over 29,000 patients, Segev et al found that obese patients on the liver transplant waiting list waited longer, and were more likely to be passed over [80], a finding seen in many other studies [81-83]. Obese patients also find more difficulty in sourcing appropriate living donors as a graft weight to recipient weight ratio of 0.8 is commonly advocated [84, 85]

The association of obesity with hypertension, diabetes, high cholesterol and sedentary lifestyle confers a 4.6 fold increased cardiovascular risk in such patients, making cardiovascular risk evaluation particularly important in this group [86]. Moreover, obese patients are more likely to have obstructive sleep apnoea, restrictive lung disease and thromboembolic disease, all of which increase risk of pulmonary hypertension.

Obese patients should be assessed by a dietician. When calculating BMI, it is important to correct for ascites volume as Leonard et al found that this correction resulted in a lower BMI classification for 11-20% of their patients [87]. Moreover, despite appearing obese, many patients awaiting liver transplant will have protein calorie malnutrition, which is associated with reduced graft and patient survival [88]. In a retrospective cohort study of 207 cirrhotic patients undergoing liver transplantation, Carias et al found that obesity was an independent predictor of pre-transplant sarcopenia (p-0.0001), and patients with NASH cirrhosis had a six-fold increased risk of sarcopaenic obesity compared to patients with other causes of cirrhosis [89]. Sometimes pre-operative weight loss is recommended in patients with compensated cirrhosis, however in view of the risk of protein-calorie malnutrition, it should not be routinely recommended in those with decompensated cirrhosis. If weight loss is attempted, it should only be under the close supervision of a dietician, and weight loss should not exceed 1kg per week [13].

The impact of obesity on patient survival and graft function after liver transplant remains uncertain (Table 1), with conflicting data in the literature possibly a reflection of selection bias as such patients have undergone rigorous evaluation prior to listing. Nair et al studied UNOS data from 18,172 patients, and found that in comparison to non-obese patients, morbid obesity (>40kg/m^2) was associated with a greater incidence of primary graft non-function, and higher mortality immediately post-transplant and at 1, 2 and 5 years afterwards, predominantly from cardiovascular causes [90]. However, other studies have reported that an elevated BMI does not confer an increased mortality risk and that the greatest concern relates to patients with low BMI [91-93]. The studies are generally small cohort studies, which differ for example in whether they distinguish between obese and morbidly obese patients. Furthermore, using BMI alone it is unclear which of patients in the studies had sarcopaenic obesity. It is likely that obesity

contributes to operative risk, but the challenge remains the quantification of that risk when summated with other risk factors, not least of which is the use of marginal grafts. Therefore, patients with obesity pre-transplant require careful evaluation and arbitrary cut-off values of BMI should be avoided.

Some studies have considered the role of bariatric surgery for patients undergoing liver transplant. Bariatric surgery could potentially be performed before, during or after the liver transplant. If bariatric surgery is performed before or after the transplant it would mean that the patient has to undergo two operations. Before the transplant, the operation would be challenging because of the concomitant coagulopathy and portal hypertension, however, achieving significant weight loss prior to transplant may confer eligibility for transplant in patients for whom it was previously contraindicated. After liver transplant, bariatric surgery would be technically challenging due to the presence of adhesions from the first operation, and because the patients will be taking immunosuppression, they have an increased risk of infection. Bariatric surgery at the time of liver transplant is feasible but there remain concerns about the combination of operations, sepsis and the availability of a specialist bariatric team.

The choices for bariatric surgery include a gastric bypass procedure, sleeve gastrectomy and gastric banding. In a small study, gastric bypass after liver transplant was associated with improved glycaemic control in patients with diabetes, achievement of weight loss, and improved lipid profile [94]. However, gastric bypass is associated with the dumping syndrome, and malabsorption, which may affect immunosuppressant medications. Furthermore, following liver transplant, some patients may require a Roux-en-Y enteric anastomosis and therefore use of non-bypass procedure is preferred. Gastric bands are relatively non-invasive, and therefore the peri-operative risk may be reduced, although they introduce a potential source of infection in an immunosuppressed group, are relatively less effective at achieving weight loss and have a surgical revision rate up to 60% [95]. Sleeve gastrectomy involves no foreign body, causes minimal malabsorption problems and is effective at achieving weight loss, rendering it the procedure of choice.

In a small study, seven patients with BMI>35 underwent combined liver transplant and sleeve gastrectomy at the time of surgery. This approach was deemed to be successful at achieving weight loss, and was associated with fewer metabolic complications after liver transplant in comparison to those who did not have gastric surgery [96]. Sleeve gastrectomy performed after liver transplant has also been shown to be effective at reducing weight and incidence of metabolic complications [97], but these studies have involved only small numbers of patients, making it difficult to draw definitive conclusions. An American study looking into feasibility and safety of sleeve gastrectomy in the perioperative period after liver transplant is currently recruiting patients and is expected to be completed by 2018 (Clinical trials identifier NCT02068872).

There are case reports of bariatric surgery following liver transplant. In one study, two patients underwent Roux-en-Y bypass for recurrent NASH in the

context of obesity which resulted in significant weight reduction, and improvement in hyperglycaemia and liver function tests [98]. In another study patients had Roux-en-Y bypass 26 months after liver transplant for cirrhosis (causes were hepatitis C (n=4), jejunal bypass surgery (n=1), haemangioendothelioma (n=1) and alcoholic liver disease (n=1)). All patients had diabetes, four had hypertension and six had dyslipidaemia. Two of the hepatitis C patients died due to multi-organ dysfunction syndrome and metastatic oesophageal cancer. In the surviving patients, there was a significant improvement in glycaemic control, reduction in BMI, and improved HDL levels [94]. The challenges of bariatric surgery in the transplant recipient are clear, but given the rising global burden of obesity it will undoubtedly become a more common occurrence.

2.2.3 NAFLD and age

In patients aged over 65 years, NASH is the most frequent indication for liver transplant [99] and notably age has been shown to be an independent predictor of poorer post-transplant outcomes [100]. According to a multivariable risk model to predict five-year survival in a large UK audit, for every one year of increased age, the hazard ratio is 1.01 [101]. As life expectancy continues to increase it is likely that older patients, who are likely to have more cardiovascular comorbidities, will be considered for transplantation, and thus input from geriatricians will be invaluable in relation to their cognitive function, functional state and risk of malignancy [100].

2.2.4 NAFLD and diabetes

NAFLD is closely associated with diabetes, which as with age has been independently associated with poor post-transplant survival, usually due to cardiovascular complications [102]. Studies show that patients with diabetes undergoing liver transplant have a longer length of hospital stay, higher 30 day re-admission rates[103], and greater incidence of renal dysfunction [104] and infection [105]. One study showed that patients with diet-controlled diabetes had comparable one and five year patient and graft survival to patients without diabetes, whereas outcomes were progressively worse for those on oral hypoglycaemic agents and insulin therapy [106]. Thus in patients with diabetes, optimisation of glycaemic control is advisable prior to transplant although there is no evidence yet that this alters outcomes.

Intraoperative glucose control is important; Parks et al found an association between intraoperative hyperglycaemia (>11.1mmol/l) during liver transplant and immediate postoperative infection (RR 2.25, confidence interval 1.26-4.03) [107]. Similarly, Amorri et al found that patients with uncontrolled intraoperative hyperglycaemia had a higher rate of infections at 30 days postoperatively compared to those with blood glucose levels <8.3mmol/l (48% vs 30%) [108]. However, intensive glycaemic control increases the risk of having life-threatening hypoglycaemia. In view of previous studies suggesting higher mortality for patients with intensive glycaemic control targets (4.5-6mmol/l) vs

conventional (<10mmol/l) targets, for example in the NICE-SUGAR trial, moderately tight glycaemic control (6-10mmol/l) is recommended [109].

2.4 Selecting appropriate donor grafts

As the prevalence of NAFLD is increasing, the proportion of donor grafts with steatosis is rising in parallel. It is now estimated that 10% of donors have steatosis greater than 30%. Graft steatosis has been shown to induce harmful microcirculatory and cellular changes, which can result in hepatocyte necrosis. Furthermore, steatosis impairs the regenerative capacity of the donor hepatocytes and has been associated with intrahepatic cholestasis and transient hyperbilirubinaemia post-transplant [110-113]. Grafts with greater than 30% steatosis have a significantly higher incidence of primary graft failure compared to those with less than 30% steatosis (13% vs <5%) [114, 115]. Donor grafts with more than 60% steatosis are often discarded, and even grafts with 30-60% steatosis are associated with reduced graft survival and higher patient mortality and hence are seldom used [116]. However, other donor characteristics are also important. One group recently reported that even with grafts obtained after brain death, provided cold ischaemia time was minimised (median 384 minutes), three year survival was comparable for grafts with steatosis<60% (n=354) and >60% steatosis (n=19) [117].

Static cold storage is widely used for organ preservation, however, steatotic livers have been shown to deteriorate quickly during hypothermic static preservation, mediated by a reduction in availability of adenosine triphosphate (ATP), with adverse outcomes [118]. An alternative technique, machine perfusion, aims to simulate a more physiological environment, with a continuous supply of nutrients and oxygen to the donor organ, and is associated with superior organ preservation in steatotic livers [119]. Furthermore, it allows a degree of resuscitation of pre-damaged organs, which offers the potential to use more marginal donors. Phase I trials of liver transplantation following normothermic machine perfusion suggest that it is safe and feasible [120].

Although liver biopsy is the gold standard for detecting steatosis, in cases of deceased liver donors, there may not be sufficient time to wait for the biopsy result. CT, Magnetic Resonance Imaging (MRI) and ultrasound are potential modalities used to quantitate the degree of steatosis. However, ultrasound is operator dependent, MRI is expensive and CT has associated radiation risks. Furthermore, these methods cannot simultaneously assess fibrosis and steatosis. Use of Controlled Attenuation Parameter as part of transient elastography can overcome these problems, and has been shown to be particularly useful in quantifying smaller degrees of steatosis [121].

3. Post-transplant considerations:

3.1 Post-transplant outcomes

US National Registry Data from the Scientific Registry of Transplant Recipients (SRTR) and UNOS indicate that for patients with NAFLD receiving a liver

transplant, one year survival is 84-89%, three year survival is 78-85%, five year survival is 77-84%, and ten year survival is 84% [8, 122, 123]. Other studies have reported that survival rates up to ten years are similar for patients receiving transplants for NAFLD and those receiving transplants for other indications (cryptogenic cirrhosis, HCV, alcoholic cirrhosis, cholestatic liver disease, and autoimmune liver disease) [8, 124]. It is important to remember that the patients who receive a transplant for NAFLD cirrhosis likely already a selected cohort, and that these results cannot be extrapolated to all patients with NAFLD who are considered for transplant.

However, the likely cause of death differs for patients with NAFLD, being more likely to be cardiovascular disease (OR 1.65; 95% CI, 1.01–2.70; $p = 0.05$) and sepsis (OR, 1.71; 95% CI, 1.17–2.50; $P = .006$), and less likely to be graft failure (OR, 0.21; 95% CI, 0.05–0.89; $P = 0.03$) [125]. The increase in transplantation for NASH cirrhosis in the US has been paralleled by an increase in cardiovascular mortality following liver transplant. Therefore, clinicians must be vigilant for identifying and aggressively treating post-transplant cardiovascular complications.

The peri-operative period is critical; some studies have shown that the 30-day mortality for patients with NAFLD is relatively high (8.5% in NAFLD patients, and 4.2% in patients without NAFLD), with death mainly related to infections and cardiac disease [126-128]. In a study by Van Wagner et al, patients with NASH cirrhosis had a higher incidence of cardiovascular events compared to those with alcoholic cirrhosis in the first year post-transplant, (26% vs 8%), particularly in the first 30 days post-transplant [129]. Over 50% of the patients who had a cardiovascular event had underlying cardiovascular risk factors such as high cholesterol or hypertension, yet only 17% and 13% of these patients were on aspirin and a statin respectively. In another study evaluating 5057 patients with NASH cirrhosis undergoing liver transplant, Van Wagner et al showed that the association between NASH cirrhosis and postoperative cardiac mortality was no longer significant after controlling for diabetes, renal impairment and pre-existing cardiovascular disease [73]. The increased cardiovascular mortality post-transplant can therefore be attributed to the high frequency of cardiovascular risk factors in patients with NASH cirrhosis.

3.2 Disease recurrence

NAFLD often recurs post-transplant, which is likely because following transplant, reduced mobility and commonly used immunosuppression regimens place patients at higher risk of developing obesity, diabetes and hypertension, or exacerbating these conditions that were previously present [124].

Diagnosing disease recurrence can be difficult as histology of the liver graft post-transplant may be affected by complications of the transplant itself, such as rejection, biliary complications and nodular regenerative hyperplasia [130].

A number of single-centre studies have tried to determine the incidence of recurrence [85, 124, 131-136], with between 8.2-92% of patients developing

recurrent NAFLD, 4-71.4% developing NASH, and 0-71.4% developing severe fibrosis by five years, with variable follow up periods ranging from a few weeks to 20 years.

NAFLD recurrence correlates significantly with higher pre- and post-transplant BMI, post-transplant triglyceride levels, and higher post-operative steroid doses [132, 134, 135, 137]. A study showed that the single nucleotide polymorphism (rs738409 on PNPLA3 gene, which mediates triglyceride hydrolysis) influences NAFLD recurrence risk [137]. Multivariate regression analysis revealed that transplant recipients with the rs738409-GG genotype had a 13.7-fold higher risk of graft steatosis than those with the rs738409-CC genotype, independent of age and post-operative weight gain.

Overall, up to ten-tears follow up, patients with NAFLD recurrence have patient and graft survival comparable to those transplanted for alcoholic liver disease, primary biliary cirrhosis and primary sclerosing cholangitis, suggesting that on the basis of current data recurrent NAFLD is not a major concern, at least in the medium term [131-133]

3.3 Development of de novo NAFLD

3.3.1 Incidence and diagnosis

Patients who have undergone liver transplantation are at risk of developing NAFLD *de novo* [138] with an incidence of 18-33% [139-142]. Liver biopsy is important for diagnosis of *de novo* NAFLD, as blood tests and imaging cannot reliably identify the presence of NASH and degree of fibrosis. In a study of 599 transplant recipients 31% of patients had *de novo* NAFLD after 40 months follow up, with NASH seen in 3.8% and advanced fibrosis or cirrhosis in 2.25%. Notably, 51% of these patients had unremarkable liver function tests [142].

3.3.2 Aetiology of de novo NAFLD post-transplant

Both host and graft factors are likely to play a role in the development of NAFD post-transplant. Post-transplant steatosis is associated with obesity, tacrolimus use, diabetes mellitus, hyperlipidaemia, arterial hypertension, alcoholic cirrhosis pre-transplant, and pre-transplant liver graft steatosis, with the prevalence of steatosis related to the number of these factors that are present [142, 143].

Patients following transplant are more likely to develop features of the metabolic syndrome [138, 139, 144, 145], with the incidence of metabolic syndrome increasing from 5% pre-transplant to 52% following liver transplant [145]. Following transplant, an estimated 65-70% of patients develop hypertension post-transplant [146], one third of patients become obese [147, 148], and 5-30% of patients develop *de novo* diabetes. Immunosuppression can contribute to the development of the metabolic syndrome, with both tacrolimus and ciclosporin also associated with nephrotoxicity, which contributes to cardiovascular risk [149]. Tacrolimus is directly associated with diabetes and NAFLD [150, 151],

whereas ciclosporin is associated with hypertension and hyperlipidaemia [152]. Steroids are associated with diabetes, hypertension and obesity.

The incidence of diabetes, obesity and graft steatosis post-transplant has been related to polymorphisms on the PNPLA3 gene of the transplant recipient [137, 153]. A polymorphism in interleukin 28B has also been associated with development of the metabolic syndrome post-transplant, but the mechanisms are less clear [154].

It is possible that the relationship between alcoholic liver cirrhosis pre-transplant, and NAFLD after transplant may also be because patients with alcoholic liver disease often also have NAFLD but because of the history of alcohol excess, the diagnosis of NAFLD was not fully considered pre-transplant.

3.3.3 Protective factors against de novo NAFLD post-transplant

Seo et al performed an analysis of 68 patients undergoing liver transplant, and found that use of ACE-inhibitors was associated with a lower risk of *de novo* NAFLD post-transplant (OR 0.09, 95% CI 0.01-0.92, p=0.042)[139], however, further data are required before recommending use of ACE inhibitors for NAFLD prevention. There is also concern that ACE inhibitors may worsen the hyperkalaemia associated with use of calcineurin inhibitors [155].

3.3.4 Consequences and evolution of de novo NAFLD post-transplant

Whilst hepatic steatosis does not predict post-transplant survival, patients that develop NAFLD are more likely to have cardiovascular events [156, 157].

In a study of patients who developed *de novo* NAFLD post-transplant, 13% regressed completely, 35% had a reduction of steatosis, 22% remained static and 30% developed worsening of the steatosis [142]. The median time between first and last biopsies was only 38 months (6-60 months), and thus data regarding long-term outcomes is required.

3.4 Management of NAFLD post-transplant

3.4.1 Choosing an appropriate immunosuppression regime

Choosing an appropriate immunosuppression regime requires weighing up the risk of unwanted side effects against the risk of graft rejection. Current regimens commonly involve combinations of steroids, calcineurin inhibitors, mTOR inhibitors and antimetabolites. The exact regimen will also be tailored according to the individual's risk of rejection, presence of renal impairment and presence of liver cancer.

Following a meta-analysis including 19 randomised controlled trials, Segev et al report that steroid-free regimens (where steroids were used ≤3months, or not at all) were associated with reduced relative risk of diabetes (RR 0.29, p<0.001), lower cholesterol levels (standard mean difference -0.41, p<0.001) and reduced

incidence of CMV infection (RR 0.52, p=0.001) with no impact on mortality, graft loss or infection rates [158]. Therefore UK guidelines recommend consideration of either a steroid-free regimen or early steroid withdrawal within three months [13].

Whilst tacrolimus and ciclosporin are associated with features of the metabolic syndrome, immunosuppression regimens free of calcineurin inhibitors are associated with a higher risk of graft rejection [159]. Tacrolimus is generally preferred over ciclosporin because it is associated with better patient outcomes, although it is important to monitor tacrolimus levels (5-8ng/ml) to achieve a balance between therapeutic effect and toxicity [160]. Use of mycophenolate rather than azathioprine allows use of a reduced tacrolimus dose, although there are concerns about a possible greater risk of late infective episodes [161].

3.4.2 Treatment of NAFLD post-transplant

There are no licensed treatments for NAFLD at present, and consequently there are no specific therapies to be considered for patients with NAFLD post-transplant. Current management includes control of diabetes, hypertension, high cholesterol and obesity. If specific treatments are developed for NAFLD, consideration will need to be given to possible interactions with immunosuppressant medications.

3.4.3 Post-transplant monitoring

Regular monitoring is important to detect disease recurrence and assess graft function. Imaging and biomarkers cannot reliably distinguish hepatitis steatosis from NASH [162-164], however, the need for liver biopsy needs to be weighed up against the procedural risks. Therefore, UK guidelines suggest that post-transplant patients have regular USS (initially at one year and then every two years), with liver biopsy recommended if the liver is found to be echo-bright [13].

It is also important to monitor and treat patients for features of the metabolic syndrome, by monitoring blood pressure, glycaemic control and lipid profile, with a target LDL cholesterol level <2.6mmol/L [13, 165].

4. Summary and Conclusions

NASH cirrhosis is becoming an increasingly common reason for liver transplant. The development of NAFLD, risk of recurrent NAFLD after transplant, and development of *de novo* NAFLD in patients transplanted for other reasons are all closely linked to the metabolic syndrome. Based on a thorough literature review, we present the following recommendations and suggestions for further work:

Careful evaluation of patients' cardiovascular risk factors pre-transplant is essential.

Patients with NAFLD often have features of the metabolic syndrome. All patients should have an ECG, ECHO, CXR and assessment of functional capacity. Patient with cardiovascular risk factors should have non-invasive testing and early discussion with a specialist to decide on the appropriateness of coronary angiography. Patients with pre-existing features of the metabolic syndrome should have these optimised prior to transplant.

The most cost-effective method of non-invasive screening for occult CAD needs to be established through further studies. Although PCI is feasible in advanced liver disease, there are increased bleeding risks in the coagulopathic patient. CABG should be avoided in advanced liver disease. Randomised controlled trials are needed to assess what degree of stenosis merits intervention for CAD pre-transplant, and whether this actually influences postoperative outcomes. Future developments may include consideration of screening for genetic polymorphisms that put patients at additional risks thus promoting a personalised approach.

Patients with renal dysfunction should be identified prior to transplant, and SLK transplant should be considered if appropriate

Pre-operatively all patients should have measurement of serum creatinine, urinalysis, quantitative protein measurement and renal ultrasound. If these are abnormal, isotopic measurement of GFR may be helpful. In the acute setting, in patients with renal dysfunction, serum creatinine should be measured daily. Based on the clinical and laboratory data pre-operative dialysis should be considered. SLK transplant should be considered in: (1) patients with end stage renal disease requiring a liver transplant (2) patients with acute kidney injury (serum creatinine >2mg/dL) on dialysis for over eight weeks (3) patients with chronic kidney disease with >30% interstitial fibrosis or >30% global glomerulosclerosis on renal biopsy.

Post-operatively, monitoring of calcineurin inhibitors is important to avoid nephrotoxicity. In view of the multiple possible aetiologies of renal impairment post-operatively, it is also important to control fluid balance, blood pressure and blood glucose.

Further work is needed to optimise methods of assessing renal dysfunction in the context of liver cirrhosis, as serum creatinine tends to overestimate GFR in this group.

3. Avoid arbitrary BMI cut off values in assessing patients who are overweight

Patients should be assessed by a dietician and should only lose weight under specialist supervision. Clinicians should be vigilant for sarcopaenic obesity. In future, bariatric surgery may play a greater role in the management of NAFLD- both in prevention and treatment.

It is not yet clear when is the best time to perform surgery, what type of surgical technique is best, and in which subset of patients this is likely to be most helpful. Data is mainly from case series, and randomised controlled trials in this area are needed. Further work could also explore the potential of newer weight loss procedures, such as endobarrier.

4. Maintain moderate glycaemic control in the perioperative period

Clinicians should aim to maintain blood sugars of 6-10mmol/l, particularly around the time of surgery, to reduce the risk of postoperative infections, whilst avoiding hypoglycaemia.

Further studies are needed to establish whether pre-operative improvement of poor glycaemic control in diabetic patients influences postoperative outcomes.

5. Be vigilant for development of the metabolic syndrome postoperatively

Patients with NASH cirrhosis are at high risk of cardiovascular events in the post-operative period. Features of the metabolic syndrome may worsen with post-operative immobility and immunosuppression. Patients with NAFLD are also more likely to suffer worsening renal function. Post-operatively, patients should have regular monitor and treatment of blood pressure, glycaemic control, lipid profile and renal function. Steroid-free immunosuppression regimes should be considered and where they are used, early withdrawal is recommended.

Further studies should establish optimal immunosuppression regimes in this group.

6. Biopsy is required to establish a diagnosis of NAFLD recurrence

Histology can help to detect recurrence of NAFLD or development of NAFLD de novo. Some pharmacological agents, such as vitamin E, may be useful in the treatment of NAFLD but their use in the post-transplant setting has not been studied and represents an area of further work. Further work is also needed to establish the long-term outcomes of NAFLD, both in patients who develop recurrent disease and in those who develop de Novo disease after transplant.

Conflicts of interest:

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PNN provided initial guidance on the article content. RSK conducted a literature review and drafted the first manuscript. PNN regularly reviewed this manuscript and advised on appropriate further reading material until the final version was produced. Both authors have approved the final article.

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Authors	Study Design	Population	Findings
Perez-Protto et al (2013) **[166]**	Single Centre Study	Normal weight, n=183 (BMI 20-26) Obese, n=47 (BMI>38)	No significant difference in patient or graft survival
Dare et al (2014) **[167]**	Single centre study	Underweight, n=8 (BMI<18.5) Normal weight, n=52 (BMI 18.5-24.9) Overweight, n=50 (BMI 25-29.9) Obese, n=53 (BMI 30- 34.9) Severely obese, n=18 (BMI 35-39.9) Morbidly obese, n=11 (BMI>40)	Increased rate of peri-operative complications and length of stay in obese group (p<0.001) No significant difference in patient or graft survival
Tanaka et al (2013) **[91]**	Single centre study	Underweight, n=58 (BMI<18.5) Normal weight, n=151 (BMI 18.5-24.9) Overweight, n=160 (BMI 25-29.9) Obese, n=92 (BMI 30- 34.9) Severely obese, n= 31 (BMI 35-39.9) Morbidly obese, n=15 (BMI>40)	Higher mortality and graft failure rate in both underweight and morbidly obese groups (p= 0.010 and p=0.038) No significant diference in length of ICU stay, length of hospital stay and postoperative vascular complications
Conzen et al (2015) **[83]**	Single centre study	Underweight, n=8 (BMI<18.5) Normal weight, n=52 (BMI 18.5-24.9) Overweight, n=50 (BMI 25-29.9) Obese, n=53 (BMI 30- 34.9) Severely obese, n=18 (BMI 35-39.9) Morbidly obese, n=11 (BMI>40)	No significant difference in ICU or hospital length of stay, operating time, or perioperative complications Morbidly obese patients had significantly lower 5 year graft (p<0.02) and patient survival (p<0.01)
Singhal et al (2015) **[168]**	Cohort, using SRTR database	Not morbidly obese, n= 12606 (BMI<40) Morbidly obese, n=416 (BMI>40)	Longer length of stay in morbidly obese patients (p<0.0001), but no significant difference in readmission rate No significant difference in graft or patient survival at 2 years

Schaeffer et al (2009) **[169]**	Single Centre Study	Non-obese, n=143 (BMI<30) Moderate obesity, n=14 (BMI 30-34) Severe obesity, n=10 (BMI>35)	Severely obese patients had a higher incidence of wound infections and dehiscence (p=0.0001) No significant difference in graft or patient survival at 1 year
Orci et al (2013) **[92]**	Cohort, using SRTR database	Underweight, n=952 (BMI<18.5) Normal weight, n=11430 (BMI 18.5-24.9) Overweight, n=13354 (BMI 25-29.9) Obese, n= 7786 (BMI 30- 34.9) Severely obese, n=3363 (BMI 35-39.9) Morbidly obese, n= 1308 (BMI>40)	Underweight patients had significantly lower post-operative survival rates
Hakeem et al (2013) **[170]**	Single Centre Study	Underweight, n=47 (BMI<18.5) Normal weight, n=643 (BMI 18.5-24.9) Overweight, n=417 (BMI 25-29.9) Obese, n=145 (BMI 30-34.9) Morbidly obese, n=73 (BMI>35)	No signification difference in patient graft survival across groups Prolonged length of stay in morbidly obese patients (p<0.001)
LaMattina et al (2012) **[82]**	Single Centre Study	Normal weight, n=216 (BMI 18-25) Overweight, n=266 (BMI 25.1-30) Class I obese, n=176 (BMI 30.1-35) Class II obese, n=83 (BMI 35.1-40) Class III obese, n=47 (BMI>40)	No signification difference in patient or graft survival across groups Prolonged operation time, higher use of blood products, longer ICU length of stay and more frequent infectious complications in obese patients
Werneck et al (2011) **[171]**	Single Centre Study	Normal weight, n=46 (BMI 18.5-24.99) Overweight, n=58 (BMI >30)	No significant difference in patient survival across groups No significant difference in ICU length of stay or necessity of NIV
Nair et al (2002) **[90]**	Cohort, using UNOS database	Non-obese, n=68 Obese (F BMI 27.3-32.3, M BMI 27.8- 31.1 Severely obese (F BMI>32.3, M BMI>31.1	Higher rate of primary non-function of graft, immediate mortality, 1-year mortality, 2-year mortality, 5-year mortality in morbidly obese group (p<0.05)
Dick et al (2009) **[172]**	Cohort, using UNOS database	Underweight, n=1827 (BMI<18.5) Control, n=68172 (BMI 18.5-40) Severely obese, n=1447 (BMI>40)	Being underweight or severely obese was associated with greater risk of death (p<0.0001)
Leonard et al (2008) **[87]**	NIDDK Liver Transplant	Underweight, n=67 (BMI<18.5) Normal weight, n=561 (BMI 18.5-25)	No significant difference in patient or graft survival across groups

	Database	Overweight, n=405 (BMI 25.1-30) Class I obese, n=178 (BMI 30.1-35) Class II obese, n=69 (BMI 35.1-40) Class III obese, n=33 (BMI>40)	
Boin et al (2007) **[173]**	Single centre study	Non-obese, n=38 (BMI<30) Obese, n=206 (BMI>30)	No significant difference in patient or graft survival across groups
Fujikawa et al (2006) **[174]**	Single Centre Study	Non-obese, n=288 (BMI<25) Obese, n=245 (BMI 25-30) Morbidly obese, n=167 (BMI >30)	No significant difference in patient or graft survival across groups
Hillingso (2005) **[175]**	Single Centre Study	Non-obese, n=20 (BMI<30) Obese , n=20 (BMI>30)	Obese patients had a higher patient mortality rate (p<0.01) No differences across the groups in length of ICU stay, use of blood products, or duration of operation
Sawyer et al (1999) **[176]**	Single Centre Study	Non-obese, n=202 (BMI <30) Obese, n=49 (BMI 30-34) Severely obese, n=26 (BMI >35)	Severely obese patients had higher rates of wound infection (p=0.0001) and death attributible to multisystem organ failure (p=0.0001) No significant difference in overall survival
Braunfeld et al (1996)**[177]**	Single centre study	Non-obese, n=61 (BMI<30) Obese, n=40 (BMI>30)	No significant difference in patient or graft survival, or post-operative complications across groups

Table 1- Summary of studies investigating the impact of obesity on liver transplant outcomes

Figure 1. Recommended pathway for pre-operative evaluation of cardiovascular risk in patients undergoing liver transplant. (CPEX: cardiopulmonary exercise testing, ECHO: echocardiogram, CT: computerised tomography, ECG: electrocardiogram, CXR: chest x-ray)